DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED VIA FACSIMILE**

Michael Friedman
Executive Vice President and Chief Operating Officer
Purdue Pharma L.P.
The Purdue Frederick Company
One Stamford Forum
201 Tresser Boulevard
Stamford, CT 06901-3431

JAN 17 2003

**RE: NDA 20-553**
**OxyContin® (oxycodone HCl controlled-release) Tablets**
**MACMIS ID# 11400**

# WARNING LETTER

Dear Mr. Friedman:

This Warning Letter (revised) concerns the dissemination of promotional materials for the marketing of OxyContin® (oxycodone HCl controlled-release) Tablets by Purdue Pharma L.P. ("Purdue"). Specifically, we refer to two journal advertisements for OxyContin that recently appeared in the *Journal of the American Medical Association* (JAMA), one in the October 2, 2002 issue (A7038) (the "October Ad") and one in the November 13, 2002 issue (A7087) (the "November Ad"). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these advertisements and has concluded that they are in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C.§§ 331(a) and (b), 352 (n), and its implementing regulations.

Your journal advertisements omit and minimize the serious safety risks associated with OxyContin, and promote it for uses beyond which have been proven safe and effective. Specifically, your journal advertisements fail to present in the body of the advertisements any information from the boxed warning in the approved product labeling (PI) for OxyContin regarding the potentially fatal risks associated with the use of OxyContin and the abuse liability of OxyContin, which is a Schedule II controlled substance, and make unsubstantiated efficacy claims promoting the use of OxyContin for pain relief. Your journal advertisements also understate the minimal safety information that is presented.

Your advertisements thus grossly overstate the safety profile of OxyContin by not referring in the body of the advertisements to serious, potentially fatal risks associated with OxyContin, thereby potentially leading to prescribing of the product based on inadequate consideration of risk. In addition, your journal advertisements fail to present in the body of the advertisements

critical information regarding limitations on the indicated use of OxyContin, thereby promoting OxyContin for a much broader range of patients with pain than are appropriate for the drug. The combination in these advertisements of suggesting such a broad use of this drug to treat pain without disclosing the potential for abuse with the drug and the serious, potentially fatal risks associated with its use, is especially egregious and alarming in its potential impact on the public health.

**Background**

OxyContin was approved on December 12, 1995. Because the drug has a potential for abuse and has risks associated with its use that are serious and potentially fatal, the current PI for OxyContin contains a boxed warning that includes the following important information (emphasis in original):

- **OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.**

- Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

- **OxyContin 80mg and 160mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.** These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

- **OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**

Because of safety concerns, there are important limitations on the indicated use of OxyContin. The boxed warning contains the following bolded statements:

- **OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.**

- **OxyContin Tablets are NOT intended for use as a prn analgesic.**

The Precautions section of the OxyContin PI contains further bolded limitations on the appropriate use of OxyContin, namely:

- **OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).**

- **OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.**

- **OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.**

- **OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.**

Moreover, because of the serious risks associated with OxyContin, it is contraindicated in a number of patient populations, including:

- Patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment)
- Patients with acute or severe bronchial asthma or hypercarbia
- Any patient who has or is suspected of having paralytic ileus.

**Lack of Important Risk Information**

Promotional materials are misleading if they fail to reveal material facts relating to potential consequences that may result from the use of the drug as recommended or suggested by the materials. Promotional materials are also misleading if they fail to include a balanced presentation of information relating to contraindications, warnings, precautions, and side effects associated with the use of a drug along with the presentation of promotional claims relating to the effectiveness and safety of the drug. Your journal advertisements are misleading because they make prominent claims of effectiveness for pain relief, but omit from the body of the advertisements crucial facts related to the serious, potentially fatal safety risks associated with the use of OxyContin, the potential for OxyContin to be abused, and the limitations on its appropriate indicated use.

Omission of material facts related to abuse liability and fatal risks

Specifically, your November Ad contains a two-page spread picturing a man fishing with a boy and featuring the prominent headline **"THERE CAN BE LIFE WITH RELIEF."** The words **"LIFE WITH RELIEF"** are the largest in the advertisement. The ad also features a graphic of two paper medication dosage cups with "8 AM" and "8 PM" next to them. The logo for OxyContin is right below, with the prominent tagline **"IT WORKS."** Your October Ad promotes **"WHEN IT'S TIME TO CONSIDER Q4-6H OPIOIDS...REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO."** The claim **"REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO"** is prominently highlighted in the middle of the ad, surrounded by comparative graphics of dosage cups which show only two dosage cups for OxyContin, as compared to six dosage cups for the other drugs. As with the November Ad, the logo for

OxyContin is directly under the graphic of the two dosage cups, with the prominent tagline "**IT WORKS**." Therefore, the principal message of both advertisements appears to be that OxyContin offers effective pain relief and has convenient dosing.

These ad presentations, however, fail to present in the body of the advertisements critical safety information related to the use of OxyContin needed to balance these broad claims promoting its efficacy for pain relief. Neither one of your ads presents in the body of the advertisements any information from the boxed warning discussing OxyContin's potential for abuse and the related considerations when prescribing the drug. Neither one of your ads presents in the body of the advertisements any information from the boxed warning disclosing that the drug can be fatal if taken by certain patients or under certain conditions. It is particularly disturbing that your November Ad would tout "Life With Relief," yet fail to warn that patients can die from taking OxyContin.

These ad presentations are accompanied by a brief summary of the prescribing information for OxyContin, including the boxed warning, and the ads include a reference to the brief summary. However, presenting important risk information in this manner is not in accordance with FDA's prescription drug advertising regulations. See 21 CFR 202.1(e)(3)(i) (Untrue or misleading information in any part of the advertisement will not be corrected by the inclusion in another distinct part of the advertisement of a brief statement containing true information relating to side effects, contraindications, and effectiveness of the drug.) The typical physician reviewing an advertisement for a prescription drug would expect the most serious risks associated with the drug to be included in the body of the ad. The body of these ads contains no discussion of the potentially fatal risks associated with the drug and its potential for abuse. Moreover, the expectation that the most relevant risks have been disclosed in the body, rather than the brief summary, of your ads is exacerbated by having a statement in the body of your ads that begins "The most serious risk..." implying that what follows is a complete statement of the drug's most serious risks, not that there are other, more serious risks to be aware of. Therefore, the language in the body of your ads reinforces the impression that the most serious risks have been disclosed, when in fact they have not.

Minimization of risk in information presented

Your ads not only omit these important risks, but also understate the minimal safety information that you do disclose in the body of the advertisements, thus completely misrepresenting the safety profile of the drug. Your ads state that "The most serious risk with opioids, including OxyContin®, is respiratory depression." This statement suggests that there are no specific safety considerations for OxyContin related to respiratory depression, which is false or misleading and could lead to prescribing of the product based on inadequate consideration of risk. This statement also fails to warn that this risk can be a fatal one. As stated in the boxed warning, OxyContin has two tablet strengths that are for use in opioid-tolerant patients only, because they can cause fatal respiratory depression when administered to patients not previously exposed to opioids. Also, the boxed warning states that OxyContin tablets are to be swallowed whole and not broken, crushed or chewed, because that leads to rapid release and absorption of a potentially fatal dose of OxyContin. It is especially troubling that your ads tout the dosing convenience of

OxyContin as a benefit, but fail to warn of these associated serious safety risks that come from its controlled-release formulation.

Your advertisements, in this context, also minimize the most common adverse events associated with OxyContin by describing "Common opioid side effects" rather than side effects and safety risks that have been seen with OxyContin itself. In addition, your advertisements state that "OxyContin is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated," without giving the specific contraindications noted above. By essentially suggesting that no safety or tolerability issues have been seen specifically with OxyContin, and by implying that OxyContin therapy is not associated with the serious and significant risks outlined above, your advertisements grossly misrepresent the safety profile of OxyContin. This implication is false or misleading and raises significant public health and safety concerns.

**Overbroadening of Indication**

Your advertisements suggest that OxyContin can be used in a much broader range of pain patients than has been proven to be safe and effective. This is even more problematic from a public health perspective given the serious safety risks associated with the drug and the serious deficiencies in the safety information presented in your advertisements.

The only indication information presented in the body of the advertisements (indeed, the only information from the boxed warning included at all as part of the body of these advertisements) is the partial language from the Indications and Usage section of the PI, "For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time," which you present by itself at the top of these advertisements. In the November Ad, this information is located in the upper left-hand corner of the picture on the first page of the spread, in small white type over a background of green leaves and blue sky. It is also the only writing on that page. This information is not prominent, and is not adequately communicated, especially in contrast to the prominent claim of "THERE CAN BE LIFE WITH RELIEF" and all the other text of the advertisement on the next page. Similarly, in the October Ad, this partial indication language is included at the top of the ad in a much smaller typesize than the prominent claims related to "effective relief" with the drug. These presentations are insufficient to give appropriate context and balance to your claims broadly promoting the use of this drug for pain relief. In addition, in your November Ad, you portray a seemingly healthy, unimpaired man out fishing and taking care of a child, rather than depicting a more typical person with persistent, moderate to severe pain taking OxyContin. Therefore your advertisements fail to adequately communicate the actual indication for OxyContin and suggest its use for pain relief in a much broader range of patients than indicated.

In addition, your advertisements fail to present in the body of the advertisements the other important limitations on the indicated use of OxyContin as noted above. Although you prominently claim effective "relief" and that the product "works," you fail to qualify that, as per the boxed warning, OxyContin is not intended to be used as a prn (as needed) analgesic. In fact, your October Ad prominently directs physicians to prescribe OxyContin "WHEN IT'S TIME TO

CONSIDER Q4-6H OPIOIDS," which could easily suggest prn use. (Q4-6H indicates 4-6 hours of effectiveness.)

Also of concern, your advertisements, and in particular, your October Ad, represent the dosing convenience of OxyContin by showing dosage cups of the type used to dispense medication in a hospital setting, along with your broad claims of efficacy. The body of the advertisements, however, fails to present the important limitations on the use of OxyContin restricting it to certain hospitalized patients, as described in the OxyContin PI. Most notably, the PI states that OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established. OxyContin is also not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time. The PI also states that OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain). You fail to present in the body of your advertisements any of these important limitations, thus suggesting the use of OxyContin in inappropriate patients.

**Conclusions and Requested Actions**

You have disseminated promotional journal advertisements that fail to disclose in the body of the advertisements serious and significant risks associated with the use of OxyContin and important limitations on the indicated use of the drug.

Because of the significant public health and safety concerns raised by your advertisements, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes:

1) Immediately ceasing the dissemination of these advertisements and all other promotional materials that contain the same or similar violations outlined in this letter.

2) Providing a plan of action to disseminate accurate and complete information to the audience(s) that received the misleading messages.

3) A written statement of your intent to comply with "1" and "2" above.

Please respond in writing to DDMAC by January 24, 2003 of your intent to comply with DDMAC's request. If you have any questions or comments, please contact Mark Askine or Carol Barstow by facsimile at 301-594-6759 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for OxyContin, and may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #11400 in addition to the ANDA number.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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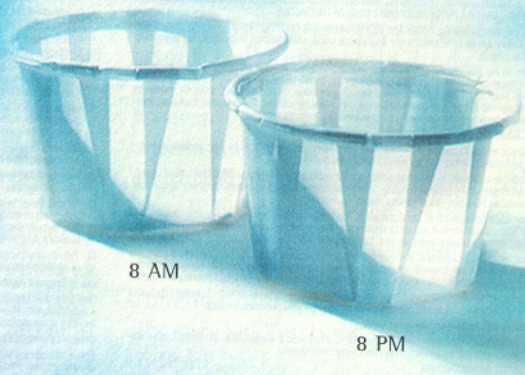
Thomas Abrams
1/17/03 04:31:31 PM

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

# WHEN IT'S TIME TO CONSIDER Q4-6H OPIOIDS...


## REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO




The most serious risk with opioids, including OxyContin®, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating and weakness.

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. (See **Contraindications** section in package insert.)

Q12h

**OxyContin® II**

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

**IT WORKS**

*Please read brief summary of full prescribing information, including boxed warning, on reverse side.*

PURDUE

Co-promoted by Purdue Pharma L.P. and Abbott Laboratories



A7038

PUR-4000956

# OxyContin® II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg 20 mg 40 mg 80 mg* 160 mg*

*80 mg and 160 mg for use in opioid-tolerant patients only

**WARNING:**

**OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.**

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

**OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.**

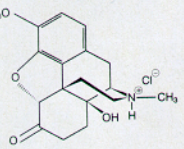
**OxyContin Tablets are NOT intended for use as a prn analgesic.**

**OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.** These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

**OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**

## DESCRIPTION

OxyContin® (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for oral administration.



## INDICATIONS AND USAGE

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

## CONTRAINDICATIONS

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

## WARNINGS

**OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**

**OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.**

**OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.**

### Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

### Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

## DRUG ABUSE AND ADDICTION

**OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.**

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

'Drug-seeking' behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated 'loss' of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). 'Doctor shopping' to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin®, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

**OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.**

### Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin®, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

### Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

### Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

## PRECAUTIONS

### General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin® is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

### Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage (⅓ to ½ of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

### Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

### Ambulatory Surgery and Postoperative Use

**OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).**

**OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.**

**OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.**

**OxyContin® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).**

Patients who are already receiving OxyContin® Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

### Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

### Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued.

### Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin® without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix 'ghosts' (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

### Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

### Drug-Drug Interactions

Opioid analgesics, including OxyContin®, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

### Use with CNS Depressants

OxyContin®, like all opioid analgesics, should be started at ⅓ to ½ of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

### Pregnancy

*Teratogenic Effects — Category B:* Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Labor and Delivery

OxyContin® is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

### Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

### Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.**

### Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15%. Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to ⅓ to ½ of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

### Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

### Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at ⅓ to ½ the usual doses and careful dose titration is warranted.

### Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

### Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

## ADVERSE REACTIONS

The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

| | OxyContin (n=227) (%) | Immediate-Release (n=225) (%) | Placebo (n=45) (%) |
|---|---|---|---|
| Constipation | (23) | (26) | (7) |
| Nausea | (23) | (27) | (11 |
| Somnolence | (23) | (24) | (4) |
| Dizziness | (13) | (16) | (9) |
| Pruritus | (13) | (12) | (2) |
| Vomiting | (12) | (14) | (7) |
| Headache | (7) | (8) | (7) |
| Dry Mouth | (6) | (7) | (2) |
| Asthenia | (6) | (7) | — |
| Sweating | (5) | (6) | (2) |

The following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

**General:** accidental injury, chest pain, facial edema, malaise, neck pain, pain

**Cardiovascular:** migraine, syncope, vasodilation, ST depression

**Digestive:** dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

**Hemic and Lymphatic:** lymphadenopathy

**Metabolic and Nutritional:** dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

**Nervous:** abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

**Respiratory:** cough increased, pharyngitis, voice alteration

**Skin:** dry skin, exfoliative dermatitis, urticaria

**Special Senses:** abnormal vision, taste perversion

**Urogenital:** amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

## OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin®, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

### Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin® may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

## SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

**CAUTION**

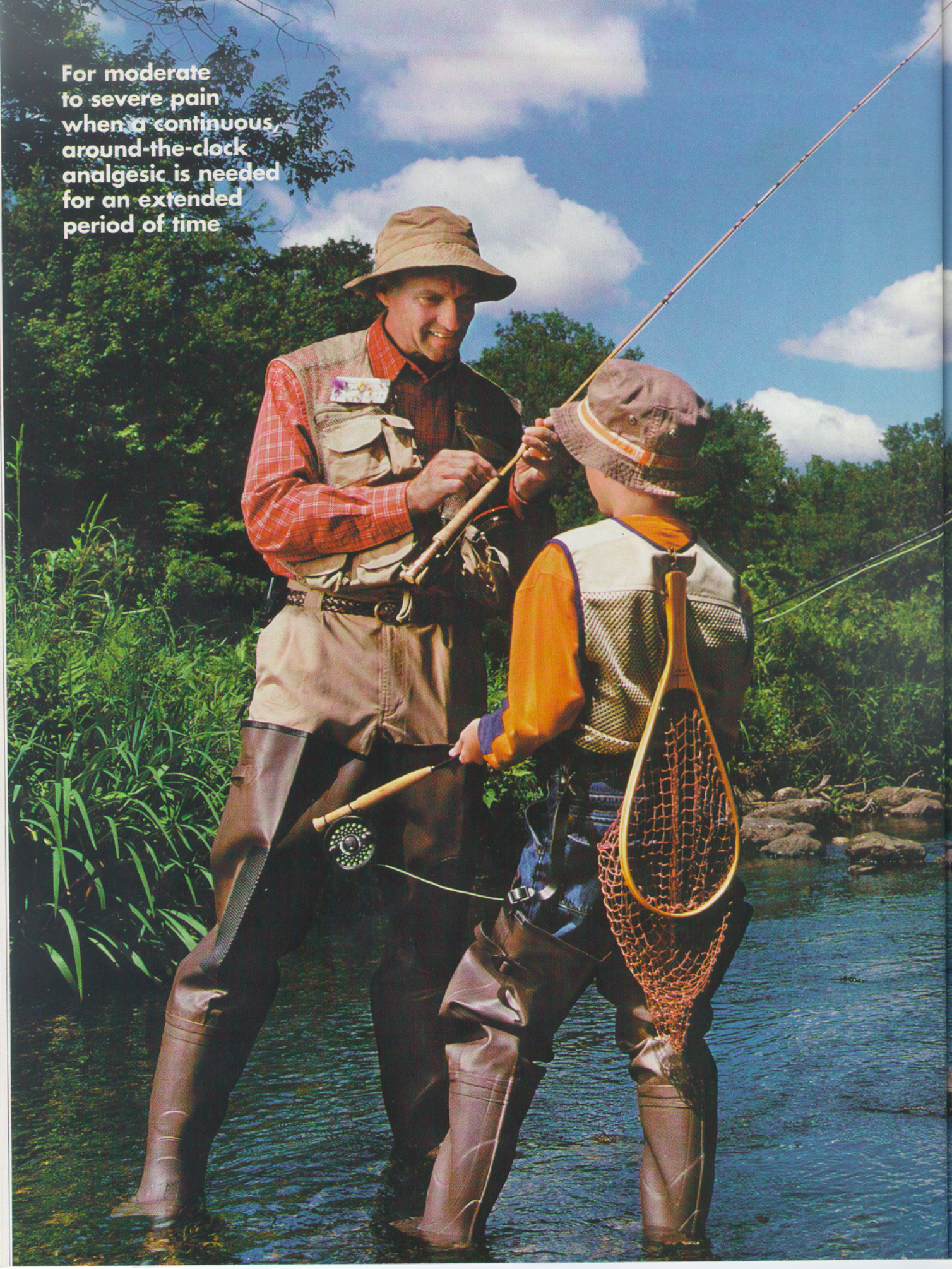
**DEA Order Form Required.**

Purdue Pharma L.P., Stamford, CT 06901-3431



U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295

July 18, 2001


For moderate
to severe pain
when a continuous,
around-the-clock
analgesic is needed
for an extended
period of time

# THERE CAN BE LIFE WITH RELIEF

The most serious risk associated with opioids, including OxyContin®, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating and weakness.

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated.

Please see **Contraindications** section in package insert.

Purdue is firmly committed to maintaining the highest standards of marketing practices in the industry while continuing to advance the proper treatment of pain in America. If Purdue's marketing and sales practices fail to meet this standard, we urge you to contact us at **1-888-690-9211.**


Q12h

OXYCONTIN® (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

IT WORKS

***Please read brief summary of prescribing information including boxed warning on reverse side.***

 A7087-FS PUR-4000927B

# OxyContin® (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg 20 mg 40 mg 80 mg* 160 mg*

*80 mg and 160 mg for use in opioid-tolerant patients only

**WARNING:**

**OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.**

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

**OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.**

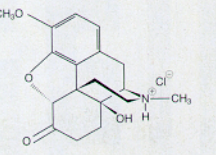
**OxyContin Tablets are NOT intended for use as a prn analgesic.**

**OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.** These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

**OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**

## DESCRIPTION

OxyContin® (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for oral administration.




## INDICATIONS AND USAGE

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

## CONTRAINDICATIONS

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

## WARNINGS

**OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**

**OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.**

**OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.**

### Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

### Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

## DRUG ABUSE AND ADDICTION

**OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.**

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

'Drug-seeking' behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated 'loss' of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). 'Doctor shopping' to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin®, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

**OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.**

### Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin®, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

### Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

### Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

## PRECAUTIONS

### General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin® is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

### Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage ($^1/_3$ to $^1/_2$ of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

### Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

### Ambulatory Surgery and Postoperative Use

**OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).**

**OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.**

**OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.**

**OxyContin® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).**

Patients who are already receiving OxyContin® Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

### Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

### Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued.

### Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin® without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix 'ghosts' (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

### Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

### Drug-Drug Interactions

Opioid analgesics, including OxyContin®, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

### Use with CNS Depressants

OxyContin®, like all opioid analgesics, should be started at $^1/_3$ to $^1/_2$ of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

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Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

### Pregnancy

*Teratogenic Effects — Category B:* Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### Labor and Delivery

OxyContin® is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

### Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

### Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.**

### Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15%. Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to $^1/_3$ to $^1/_2$ of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

### Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

### Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at $^1/_3$ to $^1/_2$ the usual doses and careful dose titration is warranted.

### Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

### Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

## ADVERSE REACTIONS

The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

| | OxyContin (n=227) (%) | Immediate-Release (n=225) (%) | Placebo (n=45) (%) |
|---|---|---|---|
| Constipation | (23) | (26) | (7) |
| Nausea | (23) | (27) | (11 |
| Somnolence | (23) | (24) | (4) |
| Dizziness | (13) | (16) | (9) |
| Pruritus | (13) | (12) | (2) |
| Vomiting | (12) | (14) | (7) |
| Headache | (7) | (8) | (7) |
| Dry Mouth | (6) | (7) | (2) |
| Asthenia | (6) | (7) | — |
| Sweating | (5) | (6) | (2) |

The following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

**General:** accidental injury, chest pain, facial edema, malaise, neck pain, pain

**Cardiovascular:** migraine, syncope, vasodilation, ST depression

**Digestive:** dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

**Hemic and Lymphatic:** lymphadenopathy

**Metabolic and Nutritional:** dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

**Nervous:** abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

**Respiratory:** cough increased, pharyngitis, voice alteration

**Skin:** dry skin, exfoliative dermatitis, urticaria

**Special Senses:** abnormal vision, taste perversion

**Urogenital:** amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

## OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin®, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

### Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalites may relieve these symptoms and should be considered.

Patients receiving OxyContin® may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

## SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

**CAUTION**

**DEA Order Form Required.**

Purdue Pharma L.P., Stamford, CT 06901-3431



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